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# Ambient Water Quality Criteria Document Addendum for 2,4-Dimethylphenol

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ADDENDUM FOR 2,4-DIMETHYLPHENOL

## Prepared for

OFFICE OF WATER REGULATIONS
AND STANDARDS

## Prepared by

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for 2, 4-Dimethylphenol.

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# PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

TABLE OF CONTENTS


| | Page |
|---|---|
| INTRODUCTION | 1 |
| REVIEW OF NEW DATA | 4 |
| Toxicologic/Carcinogenic Effects | 4 |
| Bioconcentration Factor (BCF) | 5 |
| QUANTIFICATION OF EFFECTS | 6 |
| EXISTING STANDARDS AND CRITERIA | 7 |
| REFERENCES | 8 |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| BCF | Bioconcentration factor |
| CRAVE | Carcinogen Risk Assessment Verification Endeavor |
| $LD_{50}$ | Dose lethal to 50% of recipients |
| RfD | Reference dose |

## INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multi-stage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on 2,4-dimethylphenol, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

## REVIEW OF NEW DATA

### Toxicologic/Carcinogenic Effects

New data are available that allow for the derivation of ambient water criteria for 2,4-dimethylphenol based upon health effects, thereby eliminating the need to rely upon the organoleptic data of Dietz and Traud (1978) used in the 1980 AWQCD (U.S. EPA, 1980). In a subchronic oral study by American Biogenics Corp. (1989), 2,4-dimethylphenol in corn oil was administered daily to male and female albino mice by gavage. The animals (30/sex/group) were dosed for 90 days with 5.0, 50.0 or 250 mg 2,4-dimethylphenol/kg/day. Two similar size control groups, untreated and vehicle (corn oil), were also established. Effects examined included mortality, clinical signs, body weights, food consumption, opthalmology, hematology and clinical chemistry, organ weights, gross and histopathology. Although 15 deaths occurred during this study (mostly from errors in technical procedure), only one was considered as possibly treatment-related: a male in the 5 mg/kg/day dose group died during the first 30 days of the experiment. No significant changes between treated and vehicle control groups were found in mean body weight, body weight gain, food consumption or eye examinations at any dosage. Toxicologically relevant clinical signs observed only after week 6 included squinting, lethargy, prostration and ataxia in high-dose groups of both genders, with onset shortly after dosing. Statistically significantly hematological changes included lower ($p<0.05$) mean corpuscular volume and mean corpuscular hemoglobin concentration in females of the high-dose group at terminal, but not interim, sacrifice.

At interim sacrifice in female mid- and high-dose groups, blood urea nitrogen (BUN) levels were significantly below vehicle controls; whereas at final sacrifice in the female mid-dose group, BUN levels were significantly

higher than vehicle controls. Low-dose males at interim sacrifice had significantly higher cholesterol levels. Significant differences were not found in gross necropsy or histopathological evaluations, or in organ weights, except an increase in adrenal weights of low-dose females. Based on clinical signs (lethargy, prostration and ataxia) and hematologic changes, the U.S. EPA (1990) identified 250 mg/kg/day dose as the LOAEL and 50 mg/kg/day dose as the NOAEL.

U.S. EPA (1986, 1987) described the carcinogenicity study of Boutwell and Bosch (1959), which was considered in the AWQCD (U.S. EPA, 1980). Although some evidence was obtained by Boutwell and Bosch (1959) that 2,4-dimethylphenol may be a tumor-promoting agent and that it may also act as a complete carcinogen for mouse skin, the U.S. EPA (1980, 1986, 1987) concluded that the data are insufficient to indicate that the compound is carcinogenic and that the data for the 2,4-isomer were insufficient for risk assessment. Data from the dermal route of administration were also considered inappropriate for evaluating risk associated with oral exposure (U.S. EPA, 1980).

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for 2,4-dimethylphenol is currently undergoing Agency review. The BCF value of 93.8 determined in U.S. EPA (1980) will be used until the Agency review is completed.

## QUANTIFICATION OF EFFECTS

The U.S. EPA (1980) recommended ambient water quality criterion for 2,4-dimethylphenol based upon the organoleptic data of Dietz and Traud (1978). The criterion was based upon aesthetics, as adequate data regarding the health effects of 2,4-dimethylphenol were not available at that time.

The American Biogenics Corp. (1989) study has provided pertinent information necessary to derive an oral RfD. Based on clinical signs (lethargy, prostration, ataxia and hematologic signs) the U.S. EPA identified 250 mg/kg/day as the LOAEL. Using 50 mg/kg/day as the NOAEL and applying an uncertainty factor of 3000 (100 to account for inter- and intraspecies differences, 10 for the use of a subchronic study and 3 for the lack or reproductive data in a second species) the U.S. EPA (1990) verified an oral RfD of 0.0167 mg/kg/day (rounded to 0.02 mg/kg/day).

The unrounded RfD value of 0.0167 can be used to calculate new ambient water quality criterion based upon health effects. Using the unrounded RfD and assuming an average human water consumption of 2 ℓ/day, fish consumption of 6.5 g/day, a 70 kg average adult weight and using a BCF of 93.8 ℓ/kg for 2,4-dimethylphenol, a criterion for consumption of water and fish and shellfish of 0.45 mg/ℓ is calculated. Using the same assumptions as above, a criterion for consumption of fish and shellfish alone of 1.92 mg/ℓ is calculated.

## EXISTING STANDARDS AND CRITERIA

The U.S. EPA (1990) has verified an oral RfD for 2,4-dimethylphenol of 0.02 mg/kg/day. The RfD is based on a NOAEL of 50 mg/kg/day identified from the American Biogenics Corp. (1989) study using an uncertainty factor of 3000. Dimethylphenols are classified by U.S. EPA (1987) as Group D chemicals, not classifiable as to human carcinogenicity.

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